

19



Europäisches Patentamt
European Patent Office
Office européen des brevets



11

Publication number:

0 371 431 B1

12

EUROPEAN PATENT SPECIFICATION

45

Date of publication of patent specification: **21.06.95**

51

Int. Cl.⁶: **A61K 9/18, A61K 9/20,
A61K 47/02, A61K 47/30**

21

Application number: **89121865.3**

22

Date of filing: **27.11.89**

54

Supported drugs with increased dissolution rate, and a process for their preparation.

30

Priority: **28.11.88 IT 2277088**

43

Date of publication of application:
06.06.90 Bulletin 90/23

45

Publication of the grant of the patent:
21.06.95 Bulletin 95/25

84

Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

56

References cited:
**EP-A- 0 129 893
EP-A- 0 149 197
GB-A- 2 153 678**

DIE PHARMAZIE vol. 35, no. 4, April 1980,
BERLIN DD pages 237 - 249; M. Dittgen et al:
**"Zur pharmazeutischen Technologie der
Granulierung"**

**Kobunshi Ronbunshu (Japanese Polymer
Science and Technolog)**, vol. 42, no. 11,
1985, Tokyo JP, page 828 Yasuo Nozawa et al.:
**"Increase in dissolution rates of some prac-
tically water-insoluble drugs by roll-mixing
with Polyvinylpyrrolidone"**

73

Proprietor: **VECTORPHARMA INTERNATIONAL
S.P.A.
Corso Italia, 31
I-34122 Trieste (IT)**

72

Inventor: **Lovrecich, Mara Lucia
Via Dei Moreri, 23
I-34100 Trieste (IT)**

74

Representative: **Gervasi, Gemma, Dr. et al
NOTARBARTOLO & GERVASI Srl
Viale Bianca Maria 33
I-20122 Milano (IT)**

EP 0 371 431 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

DescriptionField of the invention

5 This invention relates to supported drugs possessing characteristics which result in an increase in their rate of dissolution.

Prior art

10 It has for some time been widespread practice in the pharmaceutical field to grind or micronize poorly soluble drugs with a view to improving their biopharmaceutical properties by virtue of the resultant increase in surface area.

In addition to this general method, there has in recent years been an ongoing development in the technique of high-energy grinding, applied to mixtures comprising the drug and special support materials.

15 This technique is based on two basic elements:

1) the use of mills (of single or multi-ball type, mortar type, etc.) in which the impact or friction energy between the grinding means and the powder is particularly high;

2) the use of support materials which facilitate the desired physico-chemical transformations of the drug.

20 The primary objective of this grinding technique is the total or partial amorphization of the drug originally in the crystalline state. Amorphization results in drug solubilization kinetics having a profile involving supersaturation concentrations which are much higher than those obtainable with the drug in its crystalline state.

A further objective of this grinding technique is to improve the wettability characteristics and dissolution rate of the drug.

25 In the US Patents 3,966,899 and 4,036,990, high-energy grinding of mixtures of drugs and β -1,4-glucan is used to increase the dissolution rate of poorly soluble drugs; the product amorphization is followed by X-ray diffractometry.

30 In Japanese Patent 7986607 the support material used in the co-grinding is β -cyclodextrin, used either alone or together with other excipients such as lactose, calcium phosphate and starch, which are already present during the grinding.

β -cyclodextrin is also used in the DE Patent 3427788 to obtain inclusion complexes of benzimidazole derivatives by grinding with a ball mill. The use of microcrystalline cellulose in high-energy co-grinding is described in Chem. Pharm. Bull., 78, 3340-6, 1977; Chem. Pharm. Bull., 78, 3419-25, 1978 and Chem. Pharm. Bull., 28, 652-6, 1980; thermal analysis and IR spectrophotometry are applied in studying the support/drug interactions.

35 In the EP Patent 129893 silica gel or other adsorbent materials are used in the high-energy co-grinding of drugs such as griseofulvin, chloramphenicol and theophylline either to obtain improved dissolution rates or for amorphization.

40 The US Patent 4,639,370 describes the use of co-grinding of polymers which are swellable but insoluble in water such as cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose and dextran; the low-solubility drugs studied include medroxyprogesterone acetate, griseofulvin and indomethacin.

45 In all the preceding patents regarding high-energy co-grinding of drug-support mixtures, the procedure used is essentially to pre-mix the components and then co-grind them under dry conditions for the time required to obtain the desired amorphization and/or dissolution rate characteristics. In some cases the necessary grinding time can be particularly long, reaching and sometimes exceeding 24 hours.

Summary of the invention

50 We have now discovered a process for preparing supported drugs based on co-grinding the active substance with a support material, which has considerable advantages over the processes of the known art.

With the process according to the invention, for equal co-grinding times, the drug dissolution rate is decidedly higher, with pharmacokinetic advantages. In addition, a shorter co-grinding time is sufficient to obtain the same drug dissolution rate, thus resulting in cost advantages and the possibility of processing low-stability drugs which could degrade under prolonged co-grinding times.

55 Said process is characterised in that:

a) the active substance and support material, in the form of powders, are mixed and possibly degassed;

b) the mixture is co-ground in a mill in which the grinding chamber is saturated with the vapour of one or more solvents able to solubilize the active substance or to be adsorbed on the surface of the support material;

5 c) on termination of the co-grinding the product is dried under vacuum and sieved to eliminate any aggregates.

The products obtained by the process according to the present invention are characterised by a reduction in the residual crystallinity of the active substance indicated by a reduction in the heat of fusion, a reduction in the crystal dimensions to nanometre level indicated by a reduction in the melting point, an increase in the dissolution rate and an increase in the solubilization kinetics.

10

Detailed description of the invention

The characteristics and advantages of the supported drugs and of their preparation process according to the present invention will be more apparent from the following detailed description.

15 The active substance and the support material, both in powder form, are mixed together in a solids mixer. The active substance has a particle size distribution of between 0.01 and 1000 μm and preferably between 0.01 and 100 μm , and the support material has a particle size distribution of between 0.01 and 1000 μm and preferably between 1 and 100 μm .

20 The mixture can be heated under vacuum to a temperature compatible with the stability of the constituent substances to de-adsorb any foreign substances which may be present.

Said heating can be done in the same chamber as that in which the co-grinding is to be carried out.

The mixture obtained in this manner is introduced into the grinding chamber together with the grinding means. The chamber is connected by a valve to a storage vessel containing the relevant solvent in the gaseous state.

25 Grinding is commenced and the valve simultaneously opened so that the gaseous-phase solvent can enter the grinding chamber.

Alternatively, the grinding chamber can be pressurized with the gaseous-phase solvent by opening the connection valve immediately after introducing the mixture, the actual grinding being commenced only after a time period sufficient for the chamber to be saturated.

30 The co-grinding is conducted for a time of between 0.10 and 48 hours, and preferably between 0.25 and 4 hours.

The product obtained has a particle size distribution of between 0.01 and 100 μm .

On termination of the co-grinding operation, the mixture is placed in an oven under vacuum, or another similar apparatus, and dried at a temperature compatible with the stability of the mixture substances.

35 After drying, the product is sieved to eliminate any formed aggregates. The mill for the process according to the invention is of the type based on high impact energy between the grinding means and the powder.

Non-limiting examples of such mills are rotary mills, high vibration mills, ball mills, roller mills, mortar mills, planetary mills.

40 Many drugs are suitable for preparation by the process of the present invention, such as anti-inflammatories, analgesics, tranquilizers, sedatives, oral antitumorals. Drugs which are particularly suitable for preparation by the process of the present invention are griseofulvin, piroxicam, diacerein, diltiazem, megestrol acetate, nifedipine, nicergoline, ketoprofen, naproxen, diclofenac, ibuprofen, lorazepam, oxazepam.

45 The solvents are chosen from those which can be adsorbed by the support material and those able to act as solvents for the active substance.

By way of example, solvents suitable for use in the present invention are water, methylene chloride, chloroform, methanol, ethanol, isopropanol and their mixtures.

The support materials usable in the co-grinding for the purposes of the invention are:

- 50
- cross-linked polymers swellable in water, such as crospovidone, cross-linked polymeric cyclodextrin, cross-linked sodium carboxymethyl starch, dextran;
 - water-soluble complexing agents, such as cyclodextrin and derivatives;
 - high area and/or porosity inorganic materials such as silica gel, titanium dioxide, aluminium oxides;
 - hydrophilic linear polymers such as polyvinyl-pyrrolidone, cellulose or derivatives.

55 The weight ratio of support material to drug is between 100:1 and 1:10 and preferably between 10:1 and 1:1.

The characteristics of the products obtainable by the high-energy co-grinding technique of this invention can be defined by various methods, such as:

- determination of dissolution rate;
- determination of solubilization kinetics;
- differential scanning calorimetry to measure the heat of fusion, which is related to the residual crystallinity of the drug;
- 5 - differential scanning calorimetry or other thermoanalytical method to evaluate the reduction in melting point, which is related to the reduction of the dimensions of the drug crystals to nanometre levels.

The process according to the present invention has important advantages over the known art.

10 Firstly, a shorter co-grinding time is sufficient to attain the required degree of crystalline destructuring of the drug, with consequent considerable advantages in energy costs. In addition, a shorter co-grinding time can allow processing of low-stability drugs which could degrade under prolonged co-grinding times.

For equal co-grinding times the products obtained by the method of the invention, when compared with those obtained by the prior art, have the following advantages, existing either simultaneously or individually:

- higher degree of amorphization (lesser residual crystallinity of the drug);
- greater reduction in the dimensions of the drug crystalline residues, as far as nanometre levels, as shown by the greater lowering in the drug melting point;
- 15 - in the case of cross-linked polymeric or porous inorganic support materials there is a greater drug concentration in the surface layers of the support material;
- the dissolution rate and/or the solubilization kinetics are decidedly higher.

20 The supported drugs according to the present invention can be used in the preparation of various pharmaceutical forms such as tablets and capsules (of immediate or controlled release), suspensions, transdermic films.

For preparing immediate-release tablets or capsules they can be mixed with excipients normally used in the pharmaceutical field such as lactose, starch, calcium phosphate, microcrystalline cellulose. To prepare controlled-release tablets or capsules, said supported drugs can be mixed with polymers such as 25 methylcellulose and derivatives, polymethylmethacrylates, ethylcellulose.

The following examples of the preparation of supported drugs according to the present invention are given for purposes of illustration. The characterisation of the products obtained is given at the end of the examples.

30 EXAMPLE 1

4 g of griseofulvin and 8 g of crospovidone (Kollidon-CL, BASF) are sieved through a 60 mesh (250 μm) sieve and mixed together for 10 minutes. The mixture is placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The valve connecting the mill to a vessel containing 35 methylene chloride is opened and the grinding chamber allowed to become saturated with methylene chloride vapour.

Co-grinding is then carried out for 2 hours while maintaining saturation conditions.

On termination of co-grinding, the resultant powder has a particle size of between 1 and 100 μm .

It is dried at 30 °C under vacuum for 3 hours and then sieved through a 60 mesh (250 μm) sieve.

40 EXAMPLE 2

4 g of griseofulvin and 4 g of crospovidone are sieved through a 60 mesh (250 μm) sieve and mixed together for 10 minutes. The mixture is placed in the grinding chamber of a high-energy colloidal mill 45 together with the grinding means. The grinding chamber is saturated with vapour from methylene chloride contained in a vessel connected to the mill via a valve. Co-grinding is then carried out for 2 hours while maintaining saturation conditions.

On termination of co-grinding, the resultant powder has a particle size of between 1 and 100 μm .

50 It is dried at 30 °C under vacuum for 3 hours and then sieved through a 60 mesh (250 μm) sieve and mixed.

EXAMPLE 3

2.5 g of diacerein and 7.5 g of crospovidone are sieved through a 60 mesh (250 μm) sieve and placed 55 in the grinding chamber of a high-energy colloidal mill. The mill is operated for a few seconds to mix the powders together with the grinding means. The valve connecting the mill to a vessel containing methylene chloride is opened and the grinding chamber allowed to become saturated with the solvent vapour. Co-grinding is then carried out for 1 hour under saturation conditions. The resultant powder has a particle size

of between 1 and 100 μm .

It is dried at 30 °C under vacuum for 3 hours, sieved through a 60 mesh (250 μm) sieve and then mixed.

5 EXAMPLE 4

5 g of megestrol acetate and 10 g of crospovidone are sieved through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The chamber is then saturated with methylene chloride vapour by opening the valve connecting the mill to the vessel containing methylene chloride, and co-grinding is then carried out for 4 hours. On termination, the resultant powder has a particle size of between 1 and 100 μm . It is dried at 30 °C under vacuum for 3 hours, sieved through a 60 mesh (250 μm) sieve and then mixed.

15 EXAMPLE 5

3.5 g of megestrol acetate and 10.5 g of micronized crospovidone are sieved through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The powder is heated to 80 °C for 2 hours under vacuum. The chamber is saturated with methylene chloride vapour generated by a vessel connected to the mill via a valve, and co-grinding is then carried out for 2 hours. On termination, the resultant powder has a particle size of between 0.1 and 50 μm . It is dried at 30 °C under vacuum for 3 hours, sieved through a 60 mesh (250 μm) sieve and then mixed.

25 EXAMPLE 6

4 g of piroxicam and 12 g of micronized crospovidone are sieved through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The chamber is saturated with methylene chloride vapour generated by a vessel connected to the mill via a valve, and co-grinding is then carried out for 2 hours. On termination, the resultant powder has a particle size of between 0.1 and 50 μm . It is dried at 30 °C for 3 hours under vacuum, sieved through a 60 mesh sieve and then mixed.

EXAMPLE 7

35 4 g of megestrol acetate and 12 g of beta-cyclodextrin (CHINOIN) are sieved separately through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill. The chamber is saturated with methylene chloride vapour generated by a vessel connected to the mill via a valve, and co-grinding is then carried out for 2 hours. On termination, the resultant powder has a particle size of between 0.1 and 100 μm . It is dried at 30 °C for 3 hours under vacuum, sieved through a 60 mesh (250 μm) sieve and then mixed.

EXAMPLE 8

45 1 g of piroxicam and 9.16 g of beta-cyclodextrin are sieved separately through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The chamber is saturated with methylene chloride vapour originating from a vessel connected to the mill via a valve, and co-grinding is then carried out for 1 hour. On termination, the resultant powder has a particle size of between 0.1 and 100 μm . It is dried, sieved through a 60 mesh (250 μm) sieve and then mixed.

50 EXAMPLE 9

55 1 g of piroxicam and 3.05 g of beta-cyclodextrin are sieved separately through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The powder is heated to 80 °C for 1 hour under vacuum. The chamber is then saturated with methylene chloride vapour originating from a vessel connected to the mill via a valve, and co-grinding is carried out for 1 hour. On termination, the resultant powder has a particle size of between 0.1 and 100 μm . It is dried, sieved through a 60 mesh (250 μm) sieve and then mixed.

EXAMPLE 10

3 g of diltiazem and 9 g of polymeric beta-cyclodextrin (cross-linked with epichlorohydrin, CHINOIN) are sieved through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill. The chamber is then saturated with water vapour originating from a vessel connected to the mill via a valve, and co-grinding is carried out for 1 hour. The resultant powder has a particle size of between 1 and 100 μm . It is dried at 60 °C for 6 hours under vacuum, sieved through a 60 mesh (250 μm) sieve and then mixed.

10 EXAMPLE 11

3 g of griseofulvin and 9 g of polymeric beta-cyclodextrin (cross-linked with epichlorohydrin, CHINOIN) are sieved through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill. It is heated to 100 °C for 2 hours under vacuum, the chamber is then saturated with methylene chloride vapour originating from a vessel connected to the mill via a valve, and co-grinding carried out for 2 hours. The resultant product has a particle size of between 1 and 100 μm . It is dried, sieved through a 60 mesh (250 μm) sieve and then mixed.

EXAMPLE 12

4 g of piroxicam and 12 g of silica (Si-60, MERCK) are sieved through a 60 mesh (250 μm) sieve, mixed together and placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The chamber is saturated for 24 hours with methylene chloride vapour originating from a vessel connected to the mill via a valve, and co-grinding is then carried out for 2 hours. The resultant product has a particle size of between 0.1 and 50 μm . It is dried, sieved through a 60 mesh (250 μm) sieve and then mixed.

EXAMPLE 13

3 g of nicergoline and 9 g of crospovidone are sieved through a 60 mesh (250 μm) sieve and mixed for 10 minutes. The mixture is placed in the grinding chamber of a high-energy colloidal mill together with the grinding means. The grinding chamber is saturated with vapour from methylene chloride contained in a vessel connected to the mill via a valve. Co-grinding is then carried out for 3 hours while maintaining saturation conditions. The resultant powder has a particle size of between 1 and 100 μm . It is dried at 30 °C under vacuum for 3 hours, sieved through a 60 mesh (250 μm) sieve and mixed. The following examples of the preparation of supported drugs of the known art are provided to enable useful comparison with the preceding examples to be made. The characterisation of the obtained products is described at the end of the examples.

40 EXAMPLE A

4 g of griseofulvin and 8 g of crospovidone are co-ground exactly as described in Example 1, but without saturating the mill chamber with methylene chloride vapour.

45 EXAMPLE B

4 g of griseofulvin and 4 g of crospovidone are co-ground as described in Example 2, but without saturating the mill chamber with methylene chloride vapour.

50 EXAMPLE C

2.5 g of diacerein and 7.5 g of crospovidone are co-ground as described in Example 3, but without saturating the mill chamber with methylene chloride vapour.

55 EXAMPLE D

5 g of megestrol acetate and 10 g of crospovidone are co-ground as described in Example 4, but without saturating the mill chamber with methylene chloride vapour.

EXAMPLE E

3.5 g of megestrol acetate and 10.5 g of crospovidone are co-ground as described in Example 5, but without preheating the powder to 80 °C and without saturating the mill chamber with methylene chloride vapour.

EXAMPLE F

4 g of piroxicam and 12 g of micronized crospovidone are co-ground as described in Example 6, but without saturating the mill chamber with methylene chloride vapour.

EXAMPLE G

4 g of megestrol acetate and 12 g of beta-cyclodextrin are co-ground exactly as in Example 7, but without saturating the mill chamber with methylene chloride vapour.

EXAMPLE H

1 g of piroxicam and 9.16 g of beta-cyclodextrin are co-ground as described in Example 8, but without saturating the mill chamber with methylene chloride vapour.

EXAMPLE I

1 g of piroxicam and 3.05 g of beta-cyclodextrin are co-ground as described in Example 9, but without preheating the mixture of the two powders to 80 °C and without saturating the mill chamber with methylene chloride vapour.

EXAMPLE L

3 g of diltiazem and 9 g of cross-linked polymeric beta-cyclodextrin are co-ground as in Example 10, but without saturating the mill chamber with water vapour.

EXAMPLE M

3 g of griseofulvin and 9 g of polymeric beta-cyclodextrin (cross-linked with epichlorohydrin, CHINOIN) are co-ground as in Example 11, but without saturating the mill chamber with methylene chloride vapour.

EXAMPLE N

4 g of piroxicam and 12 g of silica SI-60 are co-ground as in Example 12, but without saturating the mill chamber with methylene chloride vapour.

CHARACTERISATION TESTS

The results are given below of characterisation tests carried out on products obtained by the process of the invention, compared with similar products obtained by the known art.

The characterisation was effected by:

- determining the dissolution rate;
- determining the solubilization kinetics;
- differential scanning calorimetry.

Determination of dissolution rate

The dissolution rate data for the supported drugs prepared by the process of this invention (Examples 1-12) are shown in Tables 1 to 9, in comparison with the dissolution rate data for the supported drugs prepared by known processes (Examples A to N).

For all the studied drugs the method used was that of USP XX No. 2, utilising a SOTAX apparatus at 37 °C and a Beckman DU 65 spectrophotometer. In all cases the sample quantities used are such as to

ensure that sink conditions (ie concentrations of 20% less than solubility) are maintained.

For products containing griseofulvin, 900 ml of a pH 7.5 buffer solution stirred at 150 r.p.m. were used; the spectrophotometric reading of suitably diluted samples was taken at 294 nm.

For products containing diacerein, 900 ml of pH 5.5 buffer solution stirred at 100 rpm. were used; the spectrophotometric reading was taken at 255 nm.

For products containing megestrol acetate, 900 ml of a pH 5.2 phosphate buffer solution stirred at 150 rpm. were used; the concentrations were determined by HPLC using a SPECTRA PHYSICS Mod. SP 4290/SP 8800 apparatus, mobile phase acetonitrile/H₂O 50/50 v/v with flow rate 1 ml/min, column NOVAPAK C₁₈, detector VV Mod. SP 8490, at 292 nm.

For products containing piroxicam, 900 ml of a pH 5.0 buffer solution stirred at 100 r.p.m. were used; the spectrophotometric reading was taken at 356 nm.

As can be seen from the data given in Tables 1-9, for all drugs and all support materials used the dissolution rate was higher for products prepared by the process of this invention than for similar products prepared by the known art.

TABLE 1

Dissolution rate of products consisting of griseofulvin/crospovidone 1:2 weight/weight		
Time	Griseofulvin concentration (µg/ml)	
	Comparison preparation (EXAMPLE A)	Preparation according to invention (EXAMPLE 1)
5 min	3.67	4.37
10 min	5.25	6.10
15 min	6.05	6.84
20 min	6.32	7.13
30 min	6.71	7.41
40 min	6.78	7.51
60 min	6.97	7.70

N.B. The reported values are the mean of at least three repeats; average C.V. 5-7%

TABLE 2

Dissolution rate of products consisting of griseofulvin/crospovidone 1:1 weight/weight		
Time	Griseofulvin concentration (µg/ml)	
	Comparison preparation (EXAMPLE B)	Preparation according to invention (EXAMPLE 2)
5 min	2.90	3.05
10 min	3.75	4.32
15 min	4.40	5.10
20 min	4.85	5.50
30 min	5.23	5.82
40 min	5.45	6.15

N.B. The reported values are the mean of at least three repeats; maximum C.V. 5-6%

TABLE 3

Dissolution rate of products consisting of diacerein/crospovidone 1:3 weight/weight		
Time	Diacerein concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE C)	Preparation according to invention (EXAMPLE 3)
1 min	9.78	11.89
3 min	13.64	19.83
5 min	15.27	23.02
10 min	17.08	24.51
15 min	18.26	25.45
30 min	19.47	26.01
45 min	21.95	25.17
60 min	23.01	26.70

N.B. The reported values are the mean of at least three repeats; average C.V. 6%

TABLE 4

Dissolution rate of products consisting of megestrol acetate/crospovidone 1:3 weight/weight		
Time	Megestrol acetate concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE E)	Preparation according to invention (EXAMPLE 5)
5 min	0.143	0.150
10 min	0.262	0.306
20 min	0.354	0.382
30 min	0.387	0.418
45 min	0.401	0.454
60 min	0.405	0.462
90 min	0.401	0.462
120 min	0.413	0.465

N.B. The reported values are the mean of at least three repeats; average C.V. 6%

TABLE 5

Dissolution rate of products consisting of piroxicam/crospovidone 1:3 weight/weight		
Time	Piroxicam concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE F)	Preparation according to invention (EXAMPLE 6)
5 min	1.11	2.09
10 min	1.77	2.70
15 min	2.23	2.88
20 min	2.53	3.01
30 min	2.61	3.03
40 min	2.72	3.03
60 min	2.72	3.24

N.B. The reported values are the mean of at least three repeats; average C.V. 6%

TABLE 6

Dissolution rate of products consisting of megestrol acetate/ β -cyclodextrin 1:3 weight/weight		
Time	Megestrol acetate concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE G)	Preparation according to invention (EXAMPLE 7)
5 min	0.017	0.033
10 min	0.028	0.056
20 min	0.048	0.108
30 min	0.0961	0.135
45 min	0.121	0.168
60 min	0.151	0.199
90 min	0.187	0.240
120 min	0.208	0.272

N.B. The reported values are the mean of at least three repeats; average C.V. 9%

TABLE 7

Dissolution rate of products consisting of piroxicam/ β -cyclodextrin 1:3 weight/weight		
Time	Piroxicam concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE I)	Preparation according to invention (EXAMPLE 9)
10 min	0.100	2.15
15 min	0.107	2.73
20 min	0.134	3.28
30 min	0.150	3.34
40 min	0.157	3.49
60 min	0.165	3.59
120 min	0.169	3.68

N.B. The reported values are the mean of at least two-three repeats; average C.V. 6%

TABLE 8

Dissolution rate of products consisting of griseofulvin/cross-linked β -cyclodextrin 1:3 weight/weight		
Time	Griseofulvin concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE M)	Preparation according to invention (EXAMPLE 11)
5 min	1.00	1.82
10 min	1.78	2.46
15 min	2.57	2.98
20 min	2.69	3.48
30 min	3.34	4.01
60 min	4.26	4.41

N.B. The reported values are the mean of two repeats; average C.V. 2-3%

TABLE 9

Dissolution rate of products consisting of piroxicam/silica gel 1:3 weight/weight		
Time	Piroxicam concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE N)	Preparation according to invention (EXAMPLE 12)
5 min	0.44	0.81
10 min	0.80	1.37
15 min	1.08	1.62
20 min	1.27	1.74
30 min	1.48	1.97
40 min	1.60	2.09
60 min	1.80	2.30
120 min	2.04	2.78

N.B. The reported values are the mean of two repeats; average C.V. 5-7%.

Determination of solubilization kinetics

The solubilization kinetics tests were conducted under non-sink conditions (ie with the drug in excess over its solubility).

For all the studied products the method used was the following: the co-ground product is placed in flasks with 40-50 ml of preheated buffer solution at the chosen pH; the flasks are placed in a CELLAI cupboard temperature-controlled at 37 °C and stirred (100-150 r.p.m.). At predetermined times an aliquot of the solution is withdrawn and filtered; the solution is then analyzed using a BECKMAN DU 65 spectrophotometer.

For products containing megestrol acetate 75 mg of product were used in 50 ml of buffer solution at pH 5.5, the spectrophotometric reading being taken at 296 nm with 4 cm cells. Stirring was at 150 r.p.m.

For products containing piroxicam 1.04 g of product were used in 40 ml of buffer solution at pH 5.0, with stirring at 100 r.p.m.. The spectrophotometric reading was taken at 356 nm.

As can be seen from the data shown in Tables 10 and 11, in all cases there was a higher solubilization kinetics for the products prepared by the processes of the present invention compared with analogous products prepared by the known art.

TABLE 10

Solubilization kinetics of products consisting of megestrol acetate/crospovidone 1:2 weight/weight		
Time	Megestrol acetate concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE D)	Preparation according to invention (EXAMPLE 4)
15 sec	5.76	6.96
30 sec	7.73	12.96
45 sec	8.80	11.19
1 min	9.01	16.21
3 min	9.95	19.50
5 min	11.71	16.38
15 min	11.74	22.19
1 hr	11.01	25.84

TABLE 11

Solubilization kinetics of products consisting of piroxicam- β -cyclodextrin 1:9.16 weight/weight		
Time	Piroxicam concentration ($\mu\text{g/ml}$)	
	Comparison preparation (EXAMPLE H)	Preparation according to invention (EXAMPLE 8)
30 sec	99.8	200.5
1 min	142.8	198.5
2 min	148.4	248.4
5 min	165.6	292.9
10 min	157.7	266.5
15 min	132.1	251.4
30 min	97.8	239.6
60 min	99.5	211.0

Differential scanning calorimeter data

A further characteristic of the products prepared by the process of this invention is that they have a high energy crystalline state characterised by a lower melting point than the drug as such and a lower heat of fusion.

The melting point depression is related to the formation of very fine crystals, in the nanometre dimensional range, and known as "nanocrystals" (F.Carli et al., Proceedings of 13th Controlled Release Bioactive Materials Symposium, Norfolk, USA, 1986; Proceedings of Ind. Pharm. Techn. Conf., London 1988).

Table 12 shows the thermoanalytical data relative to products prepared in accordance with the invention, obtained using a TA 3000 differential scanning calorimeter of Mettler (Switzerland), with nitrogen flow and a heating rate of $10^\circ\text{K min}^{-1}$. The same table also shows data relative to products prepared by the known co-grinding method, and data relative to the crystalline active principles as such. As can be seen, in all cases the products prepared in accordance with this invention have melting peaks at much lower temperatures than products prepared by known methods.

TABLE 12

Differential scanning calorimetry data for products prepared by the method of the invention and by the traditional method			
	THERMAL CHARACTERISTICS	MELTING POINT	HEAT OF FUSION
Griseofulvin as such:	only 1 peak	219.8 °C	120.4 J/g
Griseofulvin/crospovidone 1:2 weight/weight:			
Example A ^a	only 1 peak	203.4 °C	57.4 J/g
Example 1 ^b	2 peaks	204.1 °C 190.0 °C	25.8 J/g 38.7 J/g
Megestrol acetate as such:	only 1 peak	217.5 °C	83.5 J/g
Megestrol acetate/crospovidone 1:2 weight/weight:			
Example D ^a	only 1 peak	205.2 °C	34.7 J/g
Example 4 ^b	only 1 peak	193.1 °C	36.9 J/g
Megestrol acetate/ β -cyclodextrin 1:3 weight/weight:			
Example G ^a	only 1 peak	218.7 °C	83.4 J/g
Example 7 ^b	only 1 peak	215.6 °C	82.7 J/g

^a products prepared by traditional method

^b products prepared in accordance with this invention

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

- Supported drugs having a reduced heat of fusion, a reduced melting point, an increased dissolution rate and an increased solubilization kinetics obtainable by a process wherein:
 - an active substance and a support material, in the form of powders, are mixed together and possibly degassed;
 - the mixture is co-ground in a mill generating high impact energy between the grinding means and the powder in which the grinding chamber is saturated with the vapour of one or more solvents able to solubilize the active substance or to be adsorbed on the surface of the support material;
 - on termination of the co-grinding the product is dried under vacuum and sieved to eliminate any aggregates.
- Drugs as claimed in claim 1, characterized in that said active substance is an anti-inflammatory, an analgesic, a tranquilizer, a sedative or an oral antitumoral.
- Drugs as claimed in claim 1, characterized in that said active substance is griseofulvin, piroxicam, diacerein, diltiazem, megestrol acetate, nifedipine, nicergoline, ketoprofen, naproxen, diclofenac, ibuprofen, lorazepam or oxazepam.
- Drugs as claimed in claim 1, characterized in that said support material is crospovidone, cross-linked polymeric cyclodextrin, cross-linked sodium carboxymethyl starch, dextran, a cyclodextrin, high porosity silica gel, titanium dioxide or aluminium oxide, a hydrophilic linear polymer such as polyvinylpyrrolidone, cellulose or a cellulose derivative.

5. Drugs as claimed in claim 1, characterized in that the weight ratio of said support material to said active substance is between 100:1 and 1:10.
6. Drugs as claimed in claim 1, characterized in that the weight ratio of said support material to said active substance is between 10:1 and 1:1.
7. The use of drugs claimed in claims 1 to 6 in the preparation of pharmaceutical forms such as immediate-release tablets and capsules, controlled-release tablets and capsules, suspensions and transdermal films.
8. A process for preparing supported drugs claimed in claims 1 to 6 characterized in that:
a) an active substance and a support material, in the form of powders, are mixed together and possibly degassed; b) the mixture is co-ground in a mill generating high impact energy between the grinding means and the powder in which the grinding chamber is saturated with the vapour of one or more solvents able to solubilize the active substance or to be adsorbed on the surface of the support material; c) on termination of the co-grinding the product is dried under vacuum and sieved to eliminate any aggregates.
9. A process as claimed in claim 8, characterized in that said solvent is water, methylenechloride, chloroform, methanol, ethanol, isopropanol or a mixture thereof.
10. A process as claimed in claim 8, characterized in that said mill is a rotary mill, a high-vibration mill, a ball mill, a roller mill, a mortar mill or a planetary mill.
11. A process as claimed in claim 8, characterized in that said co-grinding is conducted for a time of between 0.10 and 48 hours and preferably between 0.25 and 4 hours.

Claims for the following Contracting States : ES, GR

1. A process for preparing supported drugs having a reduced heat of fusion, a reduced melting point, an increased dissolution rate and an increased solubilization kinetics, characterized in that:
a) an active substance and a support material, in the form of powders, are mixed together and possibly degassed; b) the mixture is co-ground in a mill generating high impact energy between the grinding means and the powder in which the grinding chamber is saturated with the vapour of one or more solvents able to solubilize the active substance or to be adsorbed on the surface of the support material; c) on termination of the co-grinding the product is dried under vacuum and sieved to eliminate any aggregates.
2. A process as claimed in claim 1, characterized in that said active substance is an anti-inflammatory, an analgesic, a tranquilizer, a sedative or an oral antitumoral.
3. A process as claimed in claim 1, characterized in that said active substance is griseofulvin, piroxicam, diacerein, diltiazem, megestrol acetate, nifedipine, nicergoline, ketoprofen, naproxen, diclofenac, ibuprofen, lorazepam or oxazepam.
4. A process as claimed in claim 1, characterized in that said support material is crospovidone, cross-linked polymeric cyclodextrin, cross-linked sodium carboxymethyl starch, dextran, a cyclodextrin, high porosity silica gel, titanium dioxide or aluminium oxide, a hydrophylic linear polymer such as polyvinylpyrrolidone, cellulose or a cellulose derivative.
5. A process as claimed in claim 1, characterized in that the weight ratio of said support material to said active substance is between 100:1 and 1:10.
6. A process as claimed in claim 1, characterized in that the weight ratio of said support material to said active substance is between 10:1 and 1:1.
7. A process as claimed in claim 1, characterized in that said solvent is water, methylenechloride, chloroform, methanol, ethanol, isopropanol or a mixture thereof.

8. A process as claimed in claim 1, characterized in that said mill is a rotary mill, a high-vibration mill, a ball mill, a roller mill, a mortar mill or a planetary mill.
9. A process as claimed in claim 1, characterized in that said co-grinding is conducted for a time of between 0.10 and 48 hours and preferably between 0.25 and 4 hours.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

- 10 1. Arzneimittel auf Trägern, die eine verminderte Schmelzwärme, einen erniedrigten Schmelzpunkt, eine erhöhte Lösungsgeschwindigkeit und eine erhöhte Solubilisationskinetik haben und nach einem Verfahren erhältlich sind, bei dem
- 15 a) eine aktive Substanz und ein Trägermaterial in Form von Pulvern miteinander gemischt und möglicherweise entgast werden;
- b) das Gemisch in einer Mühle gemahlen wird, die eine hohe Schlagenergie zwischen den mahlenden Mitteln und dem Pulver erzeugt und bei der die Mahlkammer mit dem Dampf von einem oder mehreren Lösungsmitteln, die geeignet sind, die aktive Substanz zu lösen oder an der Oberfläche des Trägermaterials adsorbiert zu werden, gesättigt ist;
- 20 c) das Produkt bei Beendigung des Vermahlens unter Vakuum getrocknet und zur Eliminierung irgendwelcher Aggregate gesiebt wird.
2. Arzneimittel nach Anspruch 1, dadurch **gekennzeichnet**, daß die aktive Substanz eine anti-inflammatorische Substanz, ein Analgetikum, ein Beruhigungsmittel, ein Sedativum oder ein orales Antitumor-Mittel ist.
- 25 3. Arzneimittel nach Anspruch 1, dadurch **gekennzeichnet**, daß die aktive Substanz Griseofulvin, Piroxicam, Diacerein, Diltiazem, Megestrolacetat, Nifedipin, Nicergolin, Ketoprofen, Naproxen, Diclofenac, Ibuprofen, Lorazepam oder Oxazepam ist.
- 30 4. Arzneimittel nach Anspruch 1, dadurch **gekennzeichnet**, daß das Trägermaterial Crospovidon, vernetztes polymeres Cyclodextrin, vernetzte Natrium-Carboxymethyl-Stärke, Dextran, ein Cyclodextrin, Silicagel mit hoher Porosität, Tritandioxid oder Aluminiumoxid, ein lineares, hydrophiles Polymer wie z. B. Polyvinylpyrrolidon, Cellulose oder ein Cellulosederivat ist.
- 35 5. Arzneimittel nach Anspruch 1, dadurch **gekennzeichnet**, daß das Gewichtsverhältnis Trägermaterial zu aktiver Substanz zwischen 100:1 und 1:10 liegt.
6. Arzneimittel nach Anspruch 1, dadurch **gekennzeichnet**, daß das Gewichtsverhältnis Trägermaterial zu aktiver Substanz zwischen 10:1 und 1:1 liegt.
- 40 7. Verwendung von Arzneimitteln, die in den Ansprüchen 1 bis 6 beansprucht sind, in der Herstellung pharmazeutischer Formen wie z. B. Tabletten, Kapseln, Depot-Tabletten und Depot-Kapseln, Suspensionen und transdermalen Filmen.
- 45 8. Verfahren zur Herstellung von Arzneimitteln auf Trägern, die in den Ansprüchen 1 bis 6 beansprucht sind, dadurch **gekennzeichnet**, daß
- a) eine aktive Substanz und ein Trägermaterial in Form von Pulvern miteinander gemischt und möglicherweise entgast werden;
- 50 b) das Gemisch in einer Mühle gemahlen wird, die eine hohe Schlagenergie zwischen den mahlenden Mitteln und dem Pulver erzeugt und bei der die Mahlkammer mit dem Dampf von einem oder mehreren Lösungsmitteln, die geeignet sind, die aktive Substanz zu lösen oder an der Oberfläche des Trägermaterials adsorbiert zu werden, gesättigt ist;
- c) das Produkt bei Beendigung des Vermahlens unter Vakuum getrocknet und zur Eliminierung irgendwelcher Aggregate gesiebt wird.
- 55 9. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß das Lösungsmittel Wasser, Methylenchlorid, Chloroform, Methanol, Ethanol, Isopropanol oder ein Gemisch der genannten ist.

10. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß die Mühle eine Rotationsmühle, Schwingmühle, Kugelmühle, Walzenmühle, Mörsermühle oder eine Mühle mit Planetenwalzwerk ist.
11. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß das Vermahlen über eine Zeit von zwischen 0,10 und 48 Stunden und vorzugsweise zwischen 0,25 und 4 Stunden durchgeführt wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Arzneimittel auf Trägern, die eine verminderte Schmelzwärme, einen erniedrigten Schmelzpunkt, eine erhöhte Lösungsgeschwindigkeit und eine erhöhte Solubilisationskinetik haben, dadurch **gekennzeichnet**, daß
- a) eine aktive Substanz und ein Trägermaterial in Form von Pulvern miteinander gemischt und möglicherweise entgast werden;
 - b) das Gemisch in einer Mühle gemahlen wird, die eine hohe Schlagenergie zwischen den mahlenden Mitteln und dem Pulver erzeugt und bei der die Mahlkammer mit dem Dampf von einem oder mehreren Lösungsmitteln, die geeignet sind, die aktive Substanz zu lösen oder an der Oberfläche des Trägermaterials adsorbiert zu werden, gesättigt ist;
 - c) das Produkt bei Beendigung des Vermahlens unter Vakuum getrocknet und zur Eliminierung irgendwelcher Aggregate gesiebt wird.
2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß die aktive Substanz eine anti-inflammatorische Substanz, ein Analgetikum, ein Beruhigungsmittel, ein Sedativum oder ein orales Antitumor-Mittel ist.
3. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß die aktive Substanz Griseofulvin, Piroxicam, Diacerein, Diltiazem, Megestrolacetat, Nifedipin, Nicergolin, Ketoprofen, Naproxen, Diclofenac, Ibuprofen, Lorazepam oder Oxazepam ist.
4. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß das Trägermaterial Crospovidon, vernetztes polymeres Cyclodextrin, vernetzte Natrium-Carboxymethyl-Stärke, Dextran, ein Cyclodextrin, Silicagel mit hoher Porosität, Tritandioxid oder Aluminiumoxid, ein lineares, hydrophiles Polymer wie z. B. Polyvinylpyrrolidon, Cellulose oder ein Cellulosederivat ist.
5. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß das Gewichtsverhältnis Trägermaterial zu aktiver Substanz zwischen 100:1 und 1:10 liegt.
6. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß das Gewichtsverhältnis Trägermaterial zu aktiver Substanz zwischen 10:1 und 1:1 liegt.
7. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß das Lösungsmittel Wasser, Methylenchlorid, Chloroform, Methanol, Ethanol, Isopropanol oder ein Gemisch der genannten ist.
8. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß die Mühle eine Rotationsmühle, Schwingmühle, Kugelmühle, Walzenmühle, Mörsermühle oder eine Mühle mit Planetenwalzwerk ist.
9. Verfahren nach Anspruch 8, dadurch **gekennzeichnet**, daß das Vermahlen über eine Zeit von zwischen 0,10 und 48 Stunden und vorzugsweise zwischen 0,25 und 4 Stunden durchgeführt wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Médicaments sur support ayant une chaleur de fusion réduite, un point de fusion diminué, une vitesse de dissolution augmentée et une cinétique de solubilisation augmentée, obtenus par un procédé suivant lequel :
- a) une substance active et un matériau support, sous forme de poudres, sont mélangés et dégazés si nécessaire;
 - b) le mélange est co-broyé dans un broyeur à énergie d'impact élevée entre les moyens de broyage et la poudre, dont la chambre de broyage est saturée de vapeur d'un ou plusieurs solvants capables

de solubiliser la substance active ou d'être adsorbés sur la surface du matériau support;
c) en fin de co-broyage, le produit est séché sous vide et tamisé pour éliminer tout agrégat.

2. Médicaments selon la revendication 1, caractérisés en ce que ladite substance active est un anti-inflammatoire, un analgésique, un tranquillisant, un sédatif ou un anti-tumoral oral.
3. Médicaments selon la revendication 1, caractérisés en ce que ladite substance active est la griséofulvine, le piroxicam, la diacéréine, le diltiazem, l'acétate de mégésterol, la nifédipine, la nicergoline, le kétoprofène, le naproxène, le diclofénac, l'ibuprofène, le lorazepam ou l'oxazepam.
4. Médicaments selon la revendication 1, caractérisés en ce que ledit matériau support est la crospovidone, une cyclodextrine polymère réticulée, un carboxyméthyl amidon de sodium réticulé, le dextrane, une cyclodextrine, un gel de silice à porosité élevée, le dioxyde de titane ou l'oxyde d'aluminium, un polymère linéaire hydrophile tel que la polyvinylpyrrolidone, la cellulose ou un dérivé cellulosique.
5. Médicaments selon la revendication 1, caractérisés en ce que le rapport en poids dudit matériau support à ladite substance active est entre 100:1 et 1:1.
6. Médicaments selon la revendication 1, caractérisés en ce que le rapport en poids dudit matériau support à ladite substance active est entre 10:1 et 1:1.
7. L'utilisation des médicaments selon les revendications 1 à 6 pour la préparation de formes pharmaceutiques telles que des comprimés et des gélules à libération immédiate, des comprimés et des gélules à libération contrôlée, des suspensions et des films transdermiques.
8. Procédé de préparation de médicaments sur support selon les revendications 1 à 6, caractérisé en ce que :
 - a) une substance active et un matériau support, sous forme de poudres, sont mélangés et dégazés si nécessaire;
 - b) le mélange est co-broyé dans un broyeur à énergie d'impact élevée entre les moyens de broyage et la poudre, dont la chambre de broyage est saturée de vapeur d'un ou plusieurs solvants capables de solubiliser la substance active ou d'être adsorbés sur la surface du matériau support;
 - c) en fin de co-broyage, le produit est séché sous vide et tamisé pour éliminer tout agrégat.
9. Procédé selon la revendication 8, caractérisé en ce que ledit solvant est l'eau, le chlorure de méthylène, le chloroforme, le méthanol, l'éthanol, l'isopropanol, ou un de leurs mélanges.
10. Procédé selon la revendication 8, caractérisé en ce que ledit broyeur est un broyeur rotatif, un broyeur à hautes vibrations, un broyeur à boulets, un broyeur à rouleaux, un broyeur à meules ou un broyeur planétaire.
11. Procédé selon la revendication 8, caractérisé en ce que ledit co-broyage est effectué pendant une durée entre 0,10 et 48 heures, et de préférence entre 0,25 et 4 heures.

45 **Revendications pour les Etats contractants suivants : ES, GR**

1. Procédé de préparation de médicaments sur support ayant une chaleur de fusion réduite, un point de fusion diminué, une vitesse de dissolution augmentée et une cinétique de solubilisation augmentée, caractérisé en ce que :
 - a) une substance active et un matériau support, sous forme de poudres, sont mélangés et dégazés si nécessaire;
 - b) le mélange est co-broyé dans un broyeur à énergie d'impact élevée entre les moyens de broyage et la poudre, dont la chambre de broyage est saturée de vapeur d'un ou plusieurs solvants capables de solubiliser la substance active ou d'être adsorbés sur la surface du matériau support;
 - c) en fin de co-broyage, le produit est séché sous vide et tamisé pour éliminer tout agrégat.
2. Procédé selon la revendication 1, caractérisé en ce que ladite substance active est un anti-inflammatoire, un analgésique, un tranquillisant, un sédatif ou un anti-tumoral oral.

3. Procédé selon la revendication 1, caractérisé en ce que ladite substance active est la griséofulvine, le piroxicam, la diacéréine, le diltiazem, l'acétate de mégestrol, la nifédipine, la nicergoline, le kétoprofène, le naproxène, le diclofénac, l'ibuprofène, le lorazepam ou l'oxazepam.
- 5 4. Procédé selon la revendication 1, caractérisé en ce que ledit matériau support est la crospovidone, une cyclodextrine polymère réticulée, un carboxyméthyl amidon de sodium réticulé, le dextrane, une cyclodextrine, un gel de silice à porosité élevée, le dioxyde de titane ou l'oxyde d'aluminium, un polymère linéaire hydrophile tel que la polyvinylpyrrolidone, la cellulose ou un dérivé cellulosique.
- 10 5. Procédé selon la revendication 1, caractérisé en ce que le rapport en poids dudit matériau support à ladite substance active est entre 100:1 et 1:1.
6. Procédé selon la revendication 1, caractérisé en ce que le rapport en poids dudit matériau support à ladite substance active est entre 10:1 et 1:1.
- 15 7. Procédé selon la revendication 1, caractérisé en ce que ledit solvant est l'eau, le chlorure de méthylène, le chloroforme, le méthanol, l'éthanol, l'isopropanol, ou un de leurs mélanges.
- 20 8. Procédé selon la revendication 1, caractérisé en ce que ledit broyeur est un broyeur rotatif, un broyeur à hautes vibrations, un broyeur à boulets, un broyeur à rouleaux, un broyeur à meules ou un broyeur planétaire.
9. Procédé selon la revendication 1, caractérisé en ce que ledit co-broyage est effectué pendant une durée entre 0,10 et 48 heures, et de préférence entre 0,25 et 4 heures.

25

30

35

40

45

50

55